Inorg. Chem. **2007**, *46*, 9042–9044

Iron(III) Complexes with a Biologically Relevant Aroylhydrazone: Crystallographic Evidence for Coordination Versatility

Dariusz Matoga,*,† Janusz Szklarzewicz,† Katarzyna Stadnicka,† and Musa S. Shongwe*,‡

Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Kraków, Poland, and Department of Chemistry, College of Science, Sultan Qaboos University, P.O. Box 36, Al-Khod 123, Muscat, Sultanate of Oman

Received July 20, 2007

Complexation of iron(III) with the heterodonor chelating agent 3,5-di-*tert*-butylsalicylidene benzoylhydrazine, H_2(3,5-^{t}Bu$_2$)salbh, in the absence or presence of a base affords the complex cation [Fe{H(3,5-^{t}Bu$_2$)salbh}$_2$]$^+$ or the neutral compound [Fe{H(3,5-^{t}Bu$_2$)-salbh}{(3,5-^{t}Bu$_2$)salbh}], respectively, as revealed by single-crystal X-ray analyses. Such a synthetic and crystallographic demonstration of the coordination versatility of an aroylhydrazone toward iron is uncommon. The oxidation and spin states of the iron have been verified with magnetic and spectroscopic measurements.

The siderophore desferrioxamine (DFO), produced by *Streptomyces pilosus*, is used worldwide as a chelation drug for patients suffering from iron-overload diseases or chronic iron poisoning (e.g., β-thalassemia and hemochromatosis).[1] Chelation therapy demonstrates that effective iron regulation is antitumor[2] and antimalarial[3] in humans by depriving cancer cells and malarial parasites, respectively, of iron, an essential ingredient for proliferation. The major drawback of DFO is that this drug is not orally active and, thus, has to be administered by subcutaneous infusion over extended periods of time.[4] Aroylhydrazones, such as pyridoxal isonicotinoylhydrazone (PIH) and its analogues, are increasingly recognized for their potential applications in iron chelation therapy.[2,3,5] The emergence and rapid development of these polydentate chelators underscore the urgency to produce a wide range of affordable alternative iron-chelating drugs and to design novel strategies for drug administration.

Despite the vigorous and extensive synthetic endeavors, crystallographically elucidated aroylhydrazone complexes of iron are relatively few.[6] Structural interest in such iron complexes derives primarily from the coordination versatility of the mixed-donor hydrazone ligands in terms of denticity[6c,7] and tautomerism.[8] Structural characterization is also essential to illuminating the mechanism of chelation and promoting strategies for the design and development of chelators for clinical use. Herein, we present a Communication on the X-ray crystal structures and physicochemical features of a

* To whom correspondence should be addressed. E-mail: matoga@chemia.uj.edu.pl (D.M.), musa@squ.edu.om (M.S.S.).

† Jagiellonian University.

‡ Sultan Qaboos University.

(1) (a) Hershko, C. *Baillière's Clin. Haematol.* **1994**, *7*, 965−1000. (b) Richardson, D. R. *Exp. Opin. Invest. Drugs* **1999**, *8*, 2141−2158. (c) Lovejoy, D. B.; Richardson, D. R. *Curr. Med. Chem.* **2003**, *10*, 1065−1078.

(2) (a) Lovejoy, D. B.; Richardson, D. R. *Blood* **2002**, *100*, 666−676. (b) Yuan, J.; Lovejoy, D. B.; Richardson, D. R. *Blood* **2004**, *104*, 1450−1458.

(3) (a) Hershko, C.; Peto, T. E. A. *J. Exp. Med.* **1988**, *168*, 375−387. (b) Walcourt, A.; Loyevsky, M.; Lovejoy, D. B.; Gordeuk, V. R.; Richardson, D. R. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 401−407.

(4) Giardina, P. J.; Grady, R. W.; Ehlers, K. H.; Burstein, S.; Graziano, J. H.; Marjenson, A. L.; Hilgartner, M. W. *Ann. N.Y. Acad. Sci.* **1990**, *612*, 275−285.

(5) (a) Edward, J. T.; Gauthier, M.; Chubb, F. L.; Ponka, P. *J. Chem. Eng. Data* **1988**, *33*, 538−540. (b) Link, G.; Ponka, P.; Konijn, A. M.; Breuer, W.; Cabantchik, Z. I.; Hershko, C. *Blood* **2003**, *101*, 4172−4179. (c) Richardson, D. R.; Milnes, K. *Blood* **1997**, *89*, 3025−3038.

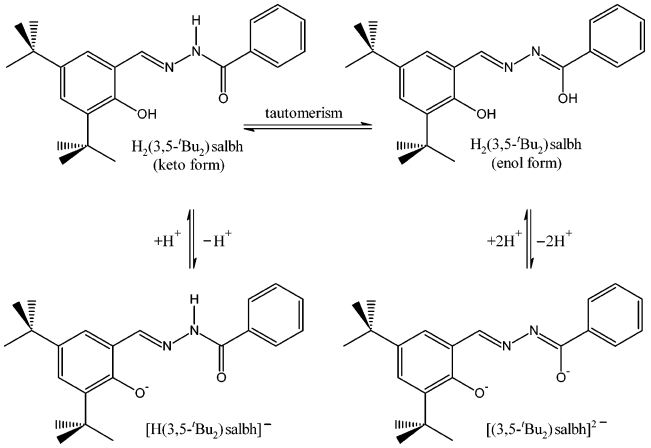
(6) (a) Aruffo, A. A.; Murphy, T. B.; Johnson, D. K.; Rose, N. J.; Schomaker, V. *Inorg. Chim. Acta* **1982**, *67*, L25−L27. (b) Murphy, T. B.; Johnson, D. K.; Rose, N. J.; Aruffo, A. A.; Schomaker, V. *Inorg. Chim. Acta* **1982**, *66*, L67−L68. (c) Bonardi, A.; Merlo, C.; Pelizzi, C.; Pelizzi, G.; Tarasconi, P.; Cavatorta, F. *J. Chem. Soc., Dalton Trans.* **1991**, 1063−1069. (d) Richardson, D. R.; Bernhardt, P. V. *J. Biol. Inorg. Chem.* **1999**, *4*, 266−273. (e) Henderson, W.; Koh, L. L.; Ranford, J. D.; Robinson, W. T.; Svensson, J. O.; Vittal, J. J.; Wang, Y. M.; Xu, Y. *J. Chem Soc., Dalton Trans.* **1999**, 3341−3344. (f) Bernhardt, P. V.; Chin, P.; Richardson, D. R. *J. Biol. Inorg. Chem.* **2001**, *6*, 801−809. (g) Bernhardt, P. V.; Caldwell, L. M.; Chaston, T. B.; Chin, P.; Richardson, D. R. *J. Biol. Inorg. Chem.* **2003**, *8*, 866−880. (h) Bernhardt, P. V.; Chin, P.; Richardson, D. R. *Dalton Trans.* **2004**, 3342−3346.

(7) (a) Bottari, B.; Maccari, R.; Monforte, F.; Ottanà, R.; Vigorita, M. G.; Bruno, G.; Nicolò, F.; Rotondo, A.; Rotondo, E. *Bioorg. Med. Chem.* **2001**, *9*, 2203−2211. (b) Naskar, S.; Mishra, D.; Chattopadhyay, S. K.; Corbella, M.; Blake, A. J. *Dalton Trans.* **2005**, 2428−2435. (c) Chen, L.; Zhang, W.; Huang, S.; Jin, X.; Sun, W.-H. *Inorg. Chem. Commun.* **2005**, *8*, 41−43. (d) Hou, J.; Sun, W.-H.; Zhang, D.; Chen, L.; Li, W.; Zhao, D.; Song, H. *J. Mol. Catal. A: Chem.* **2005**, *231*, 221−233. (e) Pelagatti, P.; Vergnani, A.; Carcelli, M.; Costa, M.; Rogolino, D.; Bacchi, A.; Pelizzi, C. *Inorg. Chim. Acta* **2003**, *351*, 235−241. (f) Pelagatti, P.; Carcelli, M.; Franchi, F.; Pelizzi, C.; Bacchi, A.; Fochi, A.; Frühauf, H.-W.; Goubitz, K.; Vrieze, K. *Eur. J. Inorg. Chem.* **2000**, 463−475. (g) Pal, S.; Pal, S. *J. Chem. Soc., Dalton Trans.* **2002**, 2102−2108. (h) Grewe, J.; Hagenbach, A.; Stromburg, B.; Alberto, R.; Vazquez-Lopez, E.; Abram, U. *Z. Anorg. Allg. Chem.* **2003**, *629*, 303−311.

(8) (a) Patole, J.; Sandbhor, U.; Padhye, S.; Deobagkar, D. N.; Anson, C. E.; Powell, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 51−55. (b) Maurya, M. R.; Agarwal, S.; Abid, M.; Azam, A.; Bader, C.; Ebel, M.; Rehder, D. *Dalton Trans.* **2006**, 937−947.

10.1021/ic701435x CCC: $37.00
Published on Web 09/25/2007

Scheme 1 . Metal- and Base-Assisted Keto−Enol Tautomerism of $H_2(3,5\text{-}^tBu_2)$salbh and Reversible Deprotonation



pair of iron(III) complexes with the potentially tridentate ligand 3,5-di-*tert*-butylsalicylidene benzoylhydrazine, $H_2(3,5\text{-}^tBu_2)$salbh (Scheme 1). Of particular importance in this current study is the crystallographic demonstration of the tautomeric maneuver of the aroylhydrazone ligand to form both cationic and neutral iron(III) complexes with the same ligand-to-iron stoichiometric ratio depending on the reaction conditions. To the best of our knowledge, such a synthetic study backed up by crystallographic analyses is not common for iron aroylhydrazones.

The ligand $H_2(3,5\text{-}^tBu_2)$salbh was produced from the condensation reaction of equimolar amounts of 3,5-di-*tert*-butylsalicylaldehyde and benzhydrazide in a refluxing mixture of equal volumes of MeOH and EtOH. Treatment of $H_2(3,5\text{-}^tBu_2)$salbh with 0.5 equiv of $FeCl_3\cdot 6H_2O$ in the presence of 2 equiv of Et_3N afforded the electrically neutral complex $[Fe\{H(3,5\text{-}^tBu_2)salbh\}\{(3,5\text{-}^tBu_2)salbh\}]\cdot EtOH\cdot H_2O$ (**1**·EtOH·H_2O) as dark brown blocks of crystals in ∼70% yield. The cationic complex $Fe\{H(3,5\text{-}^tBu_2)salbh\}_2]Cl\cdot$ 1.5MeOH·0.5EtOH (**2**·1.5MeOH·0.5EtOH) was synthesized by an analogous procedure in the absence of a base, yielding dark green blocks of crystals in ∼90% yield. The chemical compositions of these iron(III) compounds were formulated from microanalytical data[9] and subsequently verified definitively by single-crystal X-ray analyses.[10] Characteristic features of **1** and **2** readily observable in IR spectroscopy include the vibrations of the *tert*-butyl, azomethine, and amide groups. The *tert*-butyl substituent groups are conspicuous by their typical absorption patterns between 2860 and 2960 cm^{-1}, and the presence of the C═N (imine) and C═O (amide) bonds is evidenced by the prominent vibrational bands around 1590 and 1610 cm^{-1}, respectively.

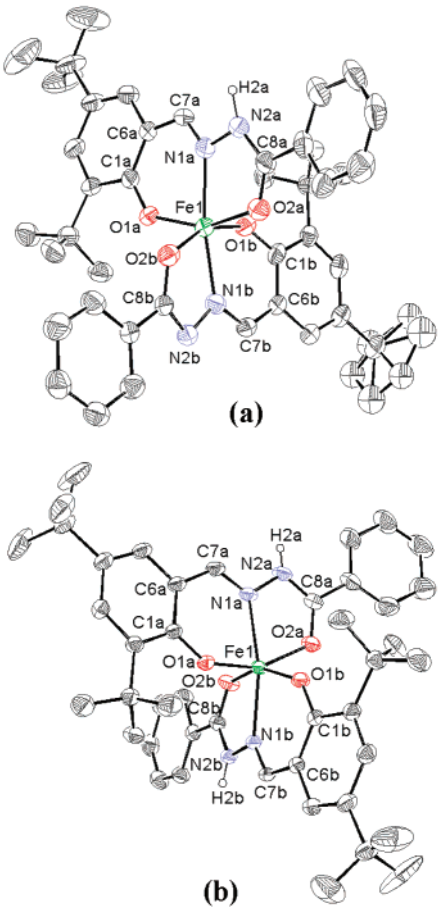


Figure 1. X-ray crystal structures of **1** and the complex cation of **2**, $[Fe\{H(3,5\text{-}^tBu_2)salbh\}_2]^{2+}$. Selected bond distances (Å) and angles (deg) for complex **1**: Fe1−N1a 2.115(6), Fe1−N1b 2.066(7), Fe1−O1a 1.900(5), Fe1−O1b 1.899(5), Fe1−O2a 2.106(6), Fe1−O2b 2.040(5), C7a−N1a 1.239(10), C7b−N1b 1.301(10), C8a−N2a 1.338(11), C8b−N2b 1.324(10), C8a−O2a 1.250(9), C8b−O2b 1.289(9); O1a−Fe1−O2a 154.4(2), O1b−Fe1−O2b 158.4(2), N1a−Fe1−N1b 169.8(3), O1a−Fe1−N1a 83.5(2), O1b−Fe1−N1b 84.3(2), O2a−Fe1−N1a 73.5(2), O2b−Fe1−N1b 75.0(2), O1a−Fe1−O1b 100.1(2), O1a−Fe1−O2b 91.9(2), O2a−Fe1−O1b 92.2(2), O2a−Fe1−O2b 84.2(2), O1a−Fe1−N1b 106.6(2), O2a−Fe1−N1b 96.9(2), O1b−Fe1−N1a 92.5(2), O2b−Fe1−N1a 106.8(2). Selected bond distances (Å) and angles (deg) for complex **2**: Fe1−N1a 2.118(2), Fe1−N1b 2.131(2), Fe1−O1a 1.898(2), Fe1−O1b 1.879(2), Fe1−O2a 2.097(2), Fe1−O2b 2.053(2), C7a−N1a 1.286(4), C7b−N1b 1.292(3), C8a−N2a 1.323(4), C8b−N2b 1.330(4), C8a−O2a 1.256(3), C8b−O2b 1.255(3); O1a−Fe1−O2a 157.07(8), O1b−Fe1−O2b 152.75(9), N1a−Fe1−N1b 164.77(9), O1a−Fe1−N1a 82.92(8), O1b−Fe1−N1b 83.26(8), O2a−Fe1−N1a 74.34(8), O2b−Fe1−N1b 74.04(8), O1a−Fe1−O1b 99.35(9), O1a−Fe1−O2b 95.99(9), O2a−Fe1−O1b 86.51(9), O2a−Fe1−O2b 88.07(9), O1a−Fe1−N1b 91.05(8), O2a−Fe1−N1b 111.72(8), O1b−Fe1−N1a 111.47(8), O2b−Fe1−N1a 92.63(8).

Complexes **1** and **2** crystallized in the monoclinic space group $P2_1/c$ and triclinic space group $P\bar{1}$, respectively.[10] The X-ray crystal structures of **1** and the complex cation of **2** are depicted in Figure 1. Four monomers, connected through a network of hydrogen bonds between the hydrazone ligands and the solvent molecules, reside in the crystallographic centrosymmetric unit cell of **1**. Each iron center exhibits a distorted octahedral geometry comprising two inequivalent tridentate ligands coordinated in a meridional fashion and

(9) Elem anal. Calcd for **1**·EtOH·H_2O: C, 67.23; H, 7.48; N, 6.82. Found: C, 66.71; H, 7.70; N, 6.79. Calcd for **2**·1.5MeOH·0.5EtOH: C, 64.54; H, 7.28; N, 6.47. Found: C, 64.17; H, 7.24; N, 6.50.

(10) Crystal data: $[Fe\{H(3,5\text{-}^tBu_2)salbh\}\{(3,5\text{-}^tBu_2)salbh\}]\cdot EtOH\cdot H_2O$ (**1**·EtOH·H_2O), $C_{46}H_{61}N_4O_6Fe$, M = 821.84, monoclinic, space group $P2_1/c$, a = 13.3760(3) Å, b = 31.0562(6) Å, c = 11.8253(2) Å, β = 91.458(1)°, U = 4910.73(17) Å^3, Z = 4, T = 293(2) K, D_c = 1.112 Mg m^{-3}, μ = 0.353 mm^{-1}, reflections measured = 10 390, reflections unique = 5522, reflections observed [$I > 2\sigma(I)$] = 3680, R1 = 0.0932, wR2 = 0.2534; $Fe\{H(3,5\text{-}^tBu_2)salbh\}_2]Cl\cdot$1.5MeOH·0.5EtOH (**2**·1.5MeOH·0.5EtOH), $C_{46.5}H_{63}N_4O_6ClFe$, M = 865.34, triclinic, space group $P\bar{1}$, a = 11.7994(2) Å, b = 13.6595(2) Å, c = 15.0346(3) Å, α = 88.266(1)°, β = 86.454(1)°, γ = 88.827(1)°, U = 2417.02(7) Å^3, Z = 2, T = 293(2) K, D_c = 1.179 Mg m^{-3}, μ = 0.414 mm^{-1}, reflections measured = 16 128, reflections unique = 10 997, reflections observed [$I > 2\sigma(I)$] = 8532, R1 = 0.0620, wR2 = 0.1602. The hydrogen atoms of the keto form of the ligand (H2a and H2b) were located from the difference Fourier map.

positioned very nearly perpendicularly to each other. Close inspection of the bond distances reveals that one of the ligands (ligand b) has undergone keto−enol tautomerism (Scheme 1). Comparison of bond distances in complex **1** shows considerable differences between the two tautomeric forms of the ligand, especially within the five-membered rings (Figure 1). The C8−O2, N1−N2, and N1−C7 bonds in the keto form (1.250, 1.387, and 1.239 Å) are shorter than the corresponding bonds in the enolate form (1.289, 1.415, and 1.301 Å), congruent with the chemical structures of both forms (Scheme 1). The enolate form (ligand b) is also found to be more strongly coordinated to the metal center with shorter Fe1−O2 and Fe1−N1 bonds (2.040 and 2.066 Å) than the corresponding ones in the keto form (ligand a; cf. 2.106 and 2.115 Å). Evidently, the double deprotonation of ligand b enhances the delocalization of electrons across the ligand framework and increases the basicity of the imine nitrogen and enolate oxygen. As expected, the relatively incompressible $Fe-O_{phenolate}$ bond is unaffected by the tautomerism. Like most six-coordinate iron(III) Schiff base complexes,[6d−g] the imine nitrogens in **1** coordinate to the metal center in trans positions; on the other hand, the phenolate oxygens occupy cis positions, as do the keto and enolate oxygens. Clearly, the electroneutrality of complex **1** was attained through the base-assisted keto−enol tautomerism. Interestingly, in the related neutral aroylhydrazone complex of iron(III) [Fe(NIH−H)(NIH−2H)][6d] (NIH = 2-hydroxy-1-naphthaldehyde isonicotinoylhydrazone), both coordinated ligands were doubly deprotonated, but one of these ligands took the form of a zwitterion with the pyridine moiety protonated. Likewise, in the complexes $[FeCl_2(PIH)]Cl$ and $[FeCl_2(PIH)(H_2O)]Cl\cdot H_2O$,[6b] the pyridine moiety acts as an internal base.

The X-ray structure of **2** consists of two discrete mononuclear complex cations. Each of the two equivalent aroylhydrazone ligands coordinates to the iron(III) ion meridionally with the phenolate oxygen, imine nitrogen, and keto oxygen donor atoms to form a pseudooctahedral geometry. Evidently, in the absence of a base, the aroylhydrazone remained in the keto form. The versatility of the coordination of $H_2(3,5\text{-}^tBu_2)$salbh to iron(III) has been shown by the formation of **1** and **2** under different reaction conditions; this property of aroylhydrazones has not been demonstrated crystallographically in this manner previously. There are no reports in the literature that show *a pair* of corresponding structurally elucidated species of iron aroylhydrazones. It is noteworthy that in both compounds **1** and **2** the $Fe-O_{phenolate}$ bonds are the strongest in the coordination sphere of the iron(III) atom, consistent with the fact that the phenonate oxygen is the most basic of the donor atoms of $H_2(3,5\text{-}^tBu_2)$-salbh. The bond distances in the coordination spheres of **1** and **2** point to the iron(III) ion being in the $^1A_{1g}$ ground state.[11]

Indeed, the room-temperature magnetic susceptibility measurements of $\mathbf{1}\cdot EtOH\cdot H_2O$ and $\mathbf{2}\cdot 1.5MeOH\cdot 0.5EtOH$ gave the effective magnetic moments [$\mu_{eff} = (8\chi_M T)^{1/2}$] 5.79 and 5.94 μ_B, respectively, consistent with a high-spin configuration ($S = {}^5/_2$) for the iron(III) center [$\mu_S = \{4S(S + 1)\}^{1/2}$].[11a,b] The spin state of these iron(III) compounds is in conformity with the moderate ligand-field strength (N_2O_4 donor set) and the bulky substituent groups. The electron paramagnetic resonance (EPR) spectra of **1** and **2** support the magnetic observation. The EPR spectrum of **1**, recorded in a frozen EtOH/MeOH (5:2, v/v) solution at 77 K, consists of an intense resonance at $g = 4.28$ and a very weak one at $g = 8.63$ (Figure 2Sa in the Supporting Information), characteristic of rhombically distorted high-spin iron(III) complexes.[11a,b,12] The EPR spectrum of **2** ($g = 4.28$ and 8.97) is very similar to that of **1**, indicative of similar coordination environments. As is usually the case with high-spin iron(III) phenolate complexes, the electronic spectra of **1** and **2** are dominated by charge-transfer absorptions in the visible region (Figure 2Sb in the Supporting Information). The higher-energy visible absorptions (shoulders at 390, 450, and 480 nm in both complexes) are associated with the phenolate (p_π) → iron(III) (d_{σ^*}) charge-transfer transitions, whereas the lower-energy absorptions [570sh ($\epsilon_{max} \sim 2200$ dm^3 mol^{-1} cm^{-1}) (**1**) and 578 nm ($\epsilon_{max} \sim 2700$ dm^3 mol^{-1} cm^{-1}) (**2**)] are attributable to phenolate (p_π) → iron(III) (d_{π^*}) charge-transfer transitions.[11,12b,c,13]

This work is presently extended to other related aroylhydrazone complexes of iron, and an investigation of the pharmacological properties of a wide range of these compounds is underway.

Acknowledgment. This work was supported by Jagiellonian University and Sultan Qaboos University (Research Grant IG/SCI/CHEM/07/04).

Supporting Information Available: CIF files for **1** and **2** and EPR and UV−vis spectra for **1** and **2** (Figure 2S). This material is available free of charge via the Internet at http://pubs.acs.org.

IC701435X

(11) (a) Shongwe, M. S.; Kaschula, C. H.; Adsetts, M. A.; Ainscough, E. W.; Brodie, A. M.; Morris, M. J. *Inorg. Chem.* **2005**, *44*, *3070*−3079. (b) McDevitt, M. R.; Addison, A. W.; Sinn, E.; Thompson, L. K. *Inorg. Chem.* **1990**, *29*, 3425−3433. (c) Lubben, M.; Meetsma, A.; van Bolhuis, F.; Feringa, B. L.; Hage, R. *Inorg. Chim. Acta* **1994**, *215*, 123−129.

(12) Oosterhuis, W. T. *Struct. Bonding* (*Berlin*) **1974**, *20*, 59−99. (b) Shongwe, M. S.; Smith, C. A.; Ainscough, E. W.; Baker, H. M.; Brodie, A. M.; Baker, E. N. *Biochemistry* **1992**, *31*, 4451−4458. (c) Shongwe, M. S.; Smith, R.; Marques, H. M.; van Wyk, J. A. *J. Inorg. Biochem.* **2004**, *98*, 199−208.

(13) (a) Gaber, B. P.; Miskowski, V.; Spiro, T. G. *J. Am. Chem. Soc.* **1974**, *96*, 6868−6873. (b) Ainscough, E. W.; Brodie, A. M.; Plowman, J. E.; Brown, K. L.; Addison, A. W.; Gainsford, A. R. *Inorg. Chem.* **1980**, *19*, 3655−3663. (c) Imbert, C.; Hratchian, H. P.; Lanznaster, M.; Heeg, M. J.; Hryhorczuk, L. M.; McGarvey, B. R.; Schlegel, H. B.; Verani, C. N. *Inorg. Chem.* **2005**, *44*, 7414−7422.